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Research Article

PREPARATION AND EVALUATION OF RETENTION TIME OF FLOATING DRUG OF PANTOPRAZOLE

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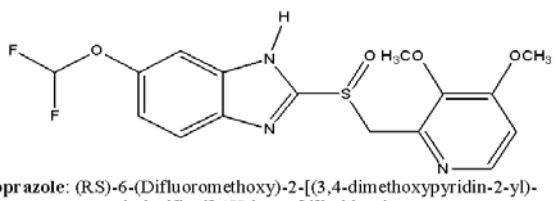
ABSTRACT

Pantoprazole is used for the treatment and management of erosion and ulceration in the stomach. It has been established that if the floating retention time of any drug is increased, the bioavailability of the drug in the stomach will also increase, and consequently the drug will be available in the stomach for long time, which can control and manage erosion and ulceration in the stomach for a long time. Hence, present study of preparation of formulation of floating drug of pantoprazole along with different polymers namely Carbomer 934 (CP), Povidone K-30 (PVP), Poly Ethylene Glycol (PEG) and Hydroxy Propyl Methyl Cellulose (HPMC) has revealed that the floating retention time of the drug has increased significantly in comparison to non-polymer floating drug. It has been observed that out of four polymers only two polymers namely Carbomer 934 (CP), Povidone K-30 (PVP) have shown excellent increase in floating retention time of the drug. Furthermore, Carbomer 934 (CP) has shown a greater increase of floating retention time. Thus, the present study is of immense importance, which will provide better formulations for the treatment of stomach and gastric ulcerative problems.

Keywords: Pantoprazole, Floating drugs, Floating retention time, Gastric ulcer, Polymers.

INTRODUCTION

Pantoprazole has been proven to be beneficial in the treatment of peptic ulcer disease when dispensed in a single unit as a core in coat tablet [1]. The floating formulations of such drugs are mainly prepared for increasing Gastro retentive property of the drug to increase the bioavailability [2, 3]. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. The drug retains the dosage form at the site of absorption and thus enhances the bioavailability. It has been reported that if the retention time of a drug in the stomach is longer time than usual (~about 8 hours), the bioavailability of the drug is enhanced [4, 5], as because the floating systems or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach [6]. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. There are several methods and systems to prepare and develop floating drugs [7], and to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner, that are less soluble in high pH environment, and gastric retention to provide new therapeutic possibilities and substantial benefits for the patients [8]. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of 1): mucoadhesion [9,10]; 2): floatation [11]; 3): sedimentation [12,13]; 4): expansion [14,15]; 5): modified shape systems [16, 17]; or by 6): the administration of pharmacological agents [18] that delay the gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs. The literature survey has revealed that the floating drug of pantoprazole with different polymers, and the study of their retention time has not been done so far by any worker, we have therefore, thought worthwhile to prepare the floating drug of pantoprazole with different polymers selected for the present study, and then to measure their retention time on UV spectrophotometer at λ_{max}291 nm for the purpose to find out the most effective polymer for preparing formulation for the enhancement of retention time of the drug in the stomach. Thus, for the present study four different polymers namely Carbomer 934 (CP), Povidone K-30 (PVP), Poly Ethylene Glycol (PEG) and Hydroxy Propyl Methyl Cellulose (HPMC) were selected and then an intimate mixture was prepared with pantoprazole in varying proportions, and then their retention time was measured on UV spectrophotometer at λ_{max}291 nm. The observation of the study has revealed that the floating retention time of the drug pantoprazole has increased significantly in comparison to non-polymer floating drug. Further, It has also been observed that out of four polymers only two polymers namely Carbomer 934 (CP) and Povidone K-30 (PVP) have shown excellent increase in floating retention time of the drug, being Carbomer 934 (CP) the most effective, which had exhibited a greater increase of floating retention time.



Pantoprazole: (RS)-6-(Difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)-methylsulfinyl]-1H-benzo[d]imidazole

MATERIALS AND METHODS

General

Source of Data collection and Literature survey

The preliminary data collection required for the experimental study and literature survey were obtained from CD-Rom search available at National Centre for Scientific Information (NCSI), National Medical Library, New Delhi; National and International Journals, Analytical chemistry, Books, Library, Relevant Books, Internet Sources and Scientific abstracts.

Methods of Collection of Data

The selected drug pantoprazole was characterized for various physicochemical properties like organoleptic properties and solubility etc.

Preparation of phosphate buffer (pH 7.4): Phosphate buffer was prepared by dissolving, a): 13.6 gm (0.2M) of potassium hydrogen phosphate (KH_2PO_4) in water, and then made up to 500 ml with distilled water. b): 4.0 gm (0.2M) NaOH was dissolved in water and then made up to 500 ml with distilled water. Then, 50 ml of above potassium hydrogen phosphate solution and 39.1 ml NaOH solution were mixed together in a volumetric flask of 200 ml and made up to the mark with distilled water, and the pH was measured by pH meter (pH at 7.4).

Preparation of sample of pantoprazole: Freshly prepared 40 ml buffer was taken in a conical flask of 200 ml and then added the sample under study (control containing only pantoprazole or sample containing pantoprazole with different ratio of polymers) and stirred on a magnetic stirrer. After 30 min 100 µl of the solution was taken in a test tube using micropipette and diluted with 10 ml of phosphate buffer. Then, the optical density/ absorbance were measured by a UV Spectrophotomer at λ_{max} 291 nm. Again, after 60 min 100 µl of the solution was taken and the same process was done to measure the optical density, and thus, 16 measurements at the intervals of 30 min were taken up to 480 min. The optical densities of control only containing pantoprazole (40 mg) and samples containing pantoprazole (40 mg) with different quantities polymers (40, 80 and 120 mg) were measured and the data have been presented in table-1. The floating retention time of each sample in presence of different polymers were then calculated.

An analytical method for estimation of drug was developed and validated using U.V Spectrophotometer (UV-1700, Shimazdu, Japan); λ_{max}: 225, 265 (sh), 291 nm (MeOH), λ_{max}: 291 nm was selected for measuring the optical density/ absorbance.

Floating capsules containing drug were prepared by using various polymers like Carbomer 934 (CP), Povidone K-30 (PVP), Poly Ethylene Glycol (PEG) and Hydroxy Propyl Methyl Cellulose (HPMC)

The various powder characteristics like bulk density, angle of repose, Carr's index, compressibility index etc were also evaluated.

The effect of polymers and their ratios on drug release have been studied.

All the data obtained were subjected for statistical analysis.

Procurement of Pantoprazole and polymers

Pantoprazole was procured by courtesy of Dr. Saji Thomas from Jubiliant Pharmaceuticals, Pvt. Ltd, New Delhi, and Carbomer 934 (CP), Povidone K-30 (PVP), Poly Ethylene Glycol (PEG) and Hydroxy Propyl Methyl Cellulose (HPMC) polymers were provided by courtesy of Dr. Farhan Jalees, Jamia Hamdard, New Delhi.

Method of preparation of pantoprazole powder blends

The pantoprazole formulations constituting different polymers were prepared by making an intimate mixture in a pestle and mortar. The accurately weighed quantity of the powder was filled in capsules.

Determination of drug content

The blended powder (100 mg) was taken in a volumetric flask containing distilled water and kept aside with constant shaking for 24 hours to extract the total drug present in the tablet. Then the absorbance of the solutions was measured after suitable dilution at λ_{max} 291 nm against drug devoid of polymer as blank control. Averages of triplicate readings were taken. The content of drug was calculated using calibration curve and the data have been presented in Table-1 and Graphs 1-7

Duration of floating time

A glass beaker containing 100 ml of 0.1N HCl was taken, in which a tablet was placed for observation. The total duration for which a tablet remains floating was recorded as duration of floatation. Average of three readings were taken and tabulated.

Study of floating retention time

The blended powder of the drug and different polymers in different proportions were taken off from the capsules and added to a phosphate buffer solution (pH 7.4) and then stirred at room temperature, after each interval of 30 min. a small quantity (100 µl) was drained out by pipette, and diluted in appropriate proportion (10 ml) with phosphate buffer (pH 7.4), and consequently the absorbance/ optical density (OD) was measured at λ_{max}: 291nm using UV Spectrophotometer. The reading of blank (control group) were also taken containing only drug without adding the polymer, total 16 reading up to 8 hrs (480 min) were taken, which have been presented in tables 1. The retention time of each formulation was calculated and a comparative analysis was also studied, which have given significant results.

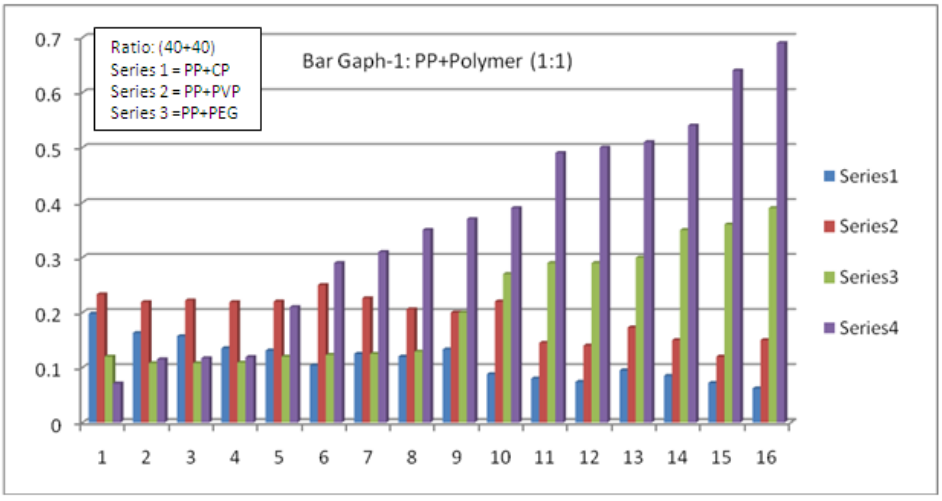
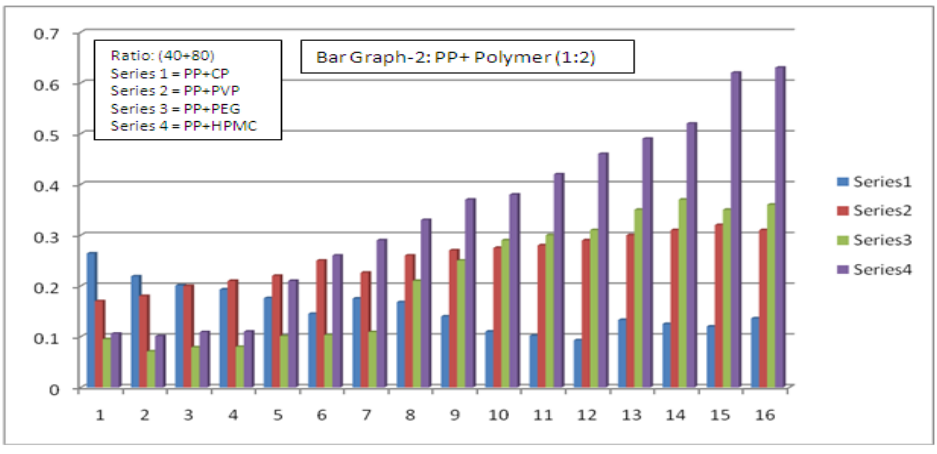
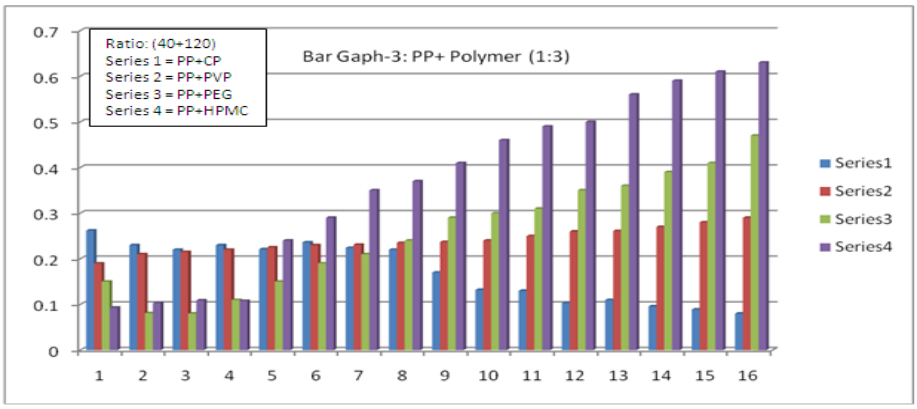


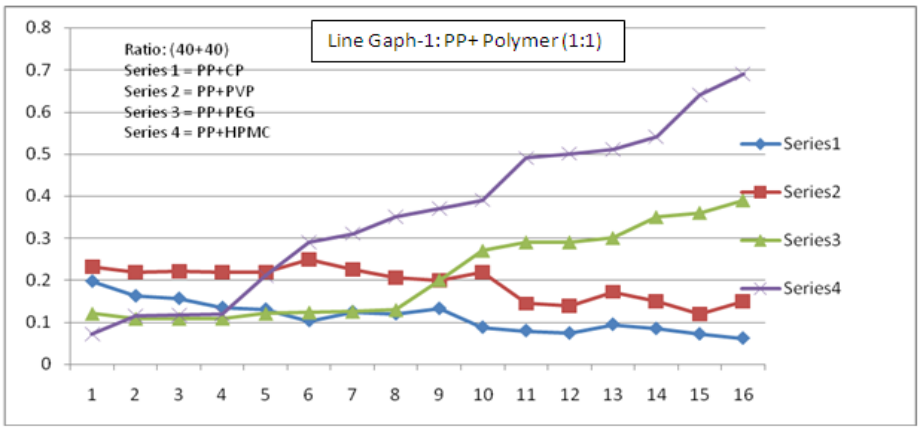
Table 1: Floating retention time at λ_{max}: 291 nm (OD: optical density)

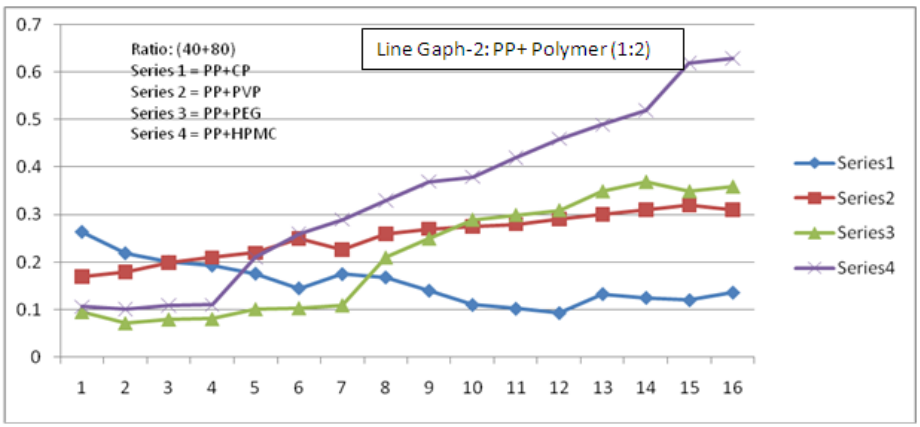
S. No.	Ratio (PP+ Polymer)	Time (min)	OD (PP) Control	OD (PP+ CP)	OD (PP+PVP)	OD (PP+PEG)	OD (PP+ HPMC-15)
1.	1:1 (40+40)	30	0.03	0.198	0.233	0.12	0.071
	1:2 (40+80)			0.264	0.17	0.095	0.106
	1:3 (40+120)			0.262	0.19	0.15	0.093
2.	1:1	60	0.043	0.163	0.219	0.108	0.115
	1:2			0.219	0.18	0.071	0.101
	1:3			0.230	0.21	0.081	0.103
3.	1:1	90	0.056	0.157	0.222	0.108	0.117
	1:2			0.201	0.2	0.079	0.109
	1:3			0.220	0.215	0.08	0.109
4.	1:1	120	0.06	0.135	0.219	0.109	0.119
	1:2			0.193	0.21	0.08	0.11
	1:3			0.230	0.22	0.11	0.108
5.	1:1	150	0.063	0.131	0.22	0.12	0.21
	1:2			0.176	0.22	0.101	0.21
	1:3			0.221	0.225	0.15	0.24
6.	1:1	180	0.08	0.104	0.25	0.123	0.29
	1:2			0.145	0.25	0.103	0.26
	1:3			0.236	0.23	0.19	0.29
7.	1:1	210	0.083	0.125	0.226	0.125	0.31
	1:2			0.175	0.226	0.109	0.29
	1:3			0.224	0.231	0.21	0.35
8.	1:1	240	0.093	0.120	0.206	0.129	0.35
	1:2			0.168	0.26	0.21	0.33
	1:3			0.220	0.235	0.24	0.37
9.	1:1	270	0.099	0.133	0.0.20	0.2	0.37
	1:2			0.140	0.27	0.25	0.37
	1:3			0.170	0.237	0.29	0.41
10	1:1	300	0.10	0.088	0.22	0.27	0.39
	1:2			0.110	0.275	0.29	0.38
	1:3			0.132	0.24	0.30	0.46
11.	1:1	330	0.11	0.080	0.145	0.29	0.49
	1:2			0.102	0.28	0.30	0.42
	1:3			0.13	0.25	0.31	0.49
12.	1:1	360	0.130	0.074	0.14	0.29	0.5
	1:2			0.093	0.29	0.31	0.46
	1:3			0.103	0.26	0.35	0.5
13.	1:1	390	0.133	0.095	0.173	0.3	0.51
	1:2			0.133	0.30	0.35	0.49
	1:3			0.110	0.261	0.36	0.56
14.	1:1	420	0.137	0.085	0.15	0.35	0.54
	1:2			0.125	0.31	0.37	0.52
	1:3			0.096	0.27	0.39	0.59
15.	1:1	450	0.140	0.072	0.12	0.36	0.64
	1:2			0.120	0.32	0.35	0.62
	1:3			0.089	0.28	0.41	0.61
16.	1:1	480	0.143	0.062	0.15	0.39	0.69
	1:2			0.136	0.31	0.36	0.63
	1:3			0.080	0.29	0.47	0.63

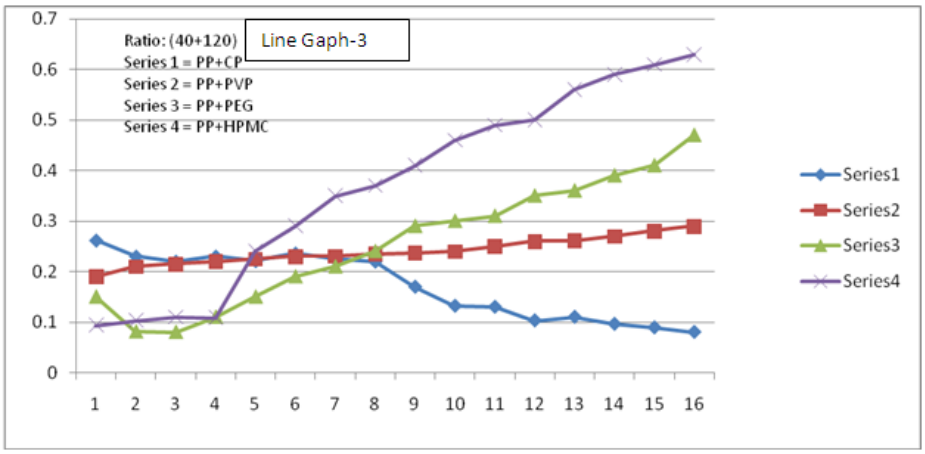
Ratio of Pantoprazole and polymers (PP + P): 1:1 (40 mg+ 40 mg); 1:2 (40 mg+ 80 mg); 1:3 (40 mg+ 120 mg); CP = Carbomer 934; PVP = Povidone K-30; PEG = Poly Ethylene Glycol; HPMPC-15 = Hydroxy Propyl Methyl Cellulose.

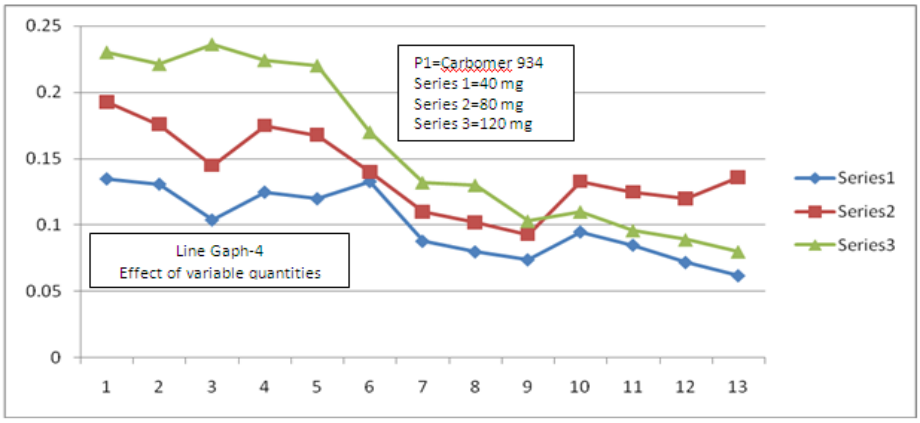


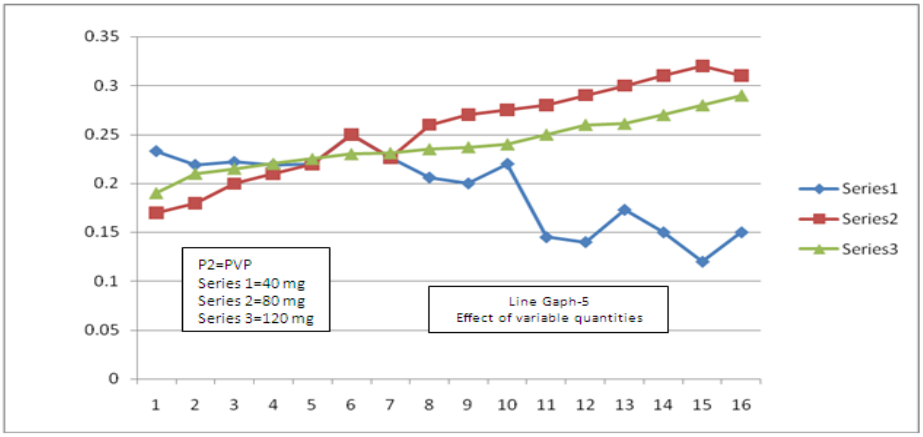

Ratio: (40+120)
Series 1 = PP+CP
Series 2 = PP+PVP
Series 3 = PP+PEG
Series 4 = PP+HPMC
Bar Gaph-3: PP+ Polymer (1:3)
Series1
Series2
Series3
Series4

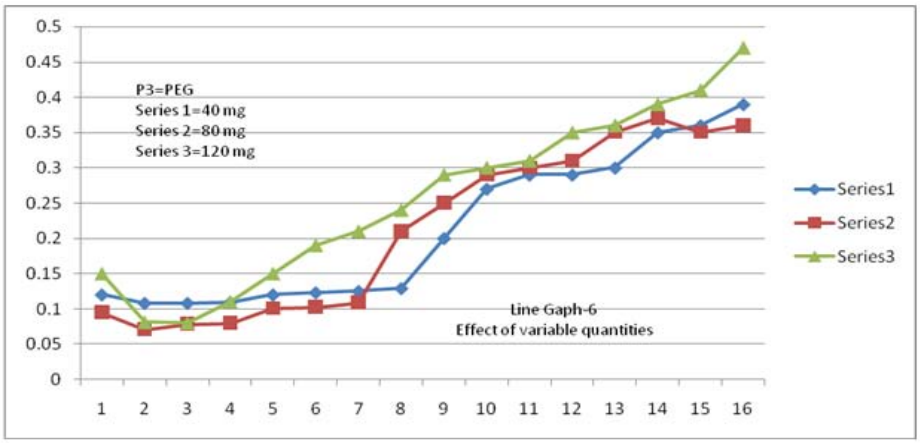

Ratio: (40+40)
Series 1 = PP+CP
Series 2 = PP+PVP
Series 3 = PP+PEG
Series 4 = PP+HPMC
Line Gaph-1: PP+ Polymer (1:1)
Series1
Series2
Series3
Series4

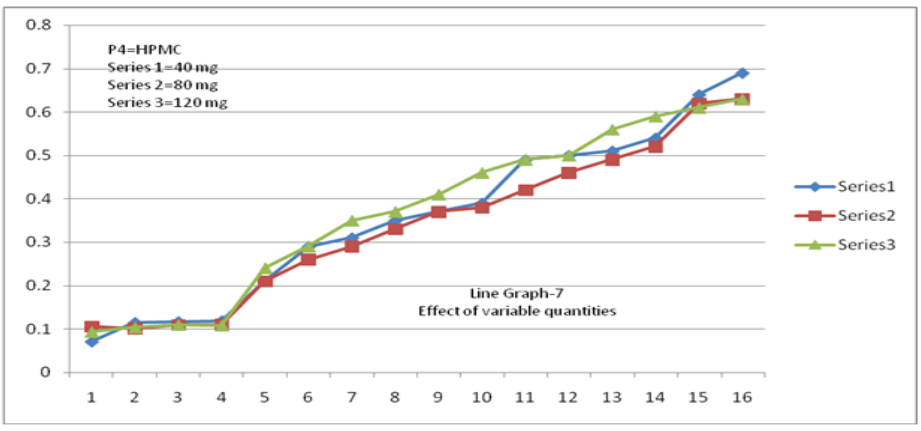

Ratio: (40+80)
Series 1 = PP+CP
Series 2 = PP+PVP
Series 3 = PP+PEG
Series 4 = PP+HPMC
Line Gaph-2: PP+ Polymer (1:2)
Series1
Series2
Series3
Series4


Ratio: (40+120)
Series 1 = PP+CP
Series 2 = PP+PVP
Series 3 = PP+PEG
Series 4 = PP+HPMC
Line Gaph-3
Series1
Series2
Series3
Series4


P1=Carbomer 934
Series 1=40 mg
Series 2=80 mg
Series 3=120 mg
Line Gaph-4
Effect of variable quantities
Series1
Series2
Series3


P2=PVP
Series 1=40 mg
Series 2=80 mg
Series 3=120 mg
Line Gaph-5
Effect of variable quantities
Series1
Series2
Series3


P3=PEG
Series 1=40 mg
Series 2=80 mg
Series 3=120 mg
Line Gaph-6
Effect of variable quantities
Series1
Series2
Series3


P4=HPMC
Series 1=40 mg
Series 2=80 mg
Series 3=120 mg
Line Graph-7
Effect of variable quantities
Series1
Series2
Series3

RESULTS AND DISCUSSION

Pantoprazole is metabolized in the liver by the cytochrome p450 system [19]. Metabolism mainly consists of demethylation by CYP2C19 followed by sulfation. Another metabolic pathway is oxidation by CYP3A4. Pantoprazole metabolites are not thought to have any pharmacological significance. It is relatively free of drug interactions [20]. Pantoprazole binds irreversibly to H+K+ATPase (proton pumps) and suppresses the secretion of acid. As it binds irreversibly to the pumps, new pumps have to be made before acid production can be resumed. The drug's plasma half-life is about 2 hours [21]. The formulations of floating drugs of pantoprazole were prepared in combination with different polymers in varying proportions. The increase/decrease in retention time was measured at λ_{max} 291 nm by using UV Spectrophotometer. The absorbance is directly proportional to the concentration of the drug. The present study measures the absorbance of each formulation, which indicated the decrease of absorbance with time of intervals of 30 min to 480 min, which consequently suggested the decrease of concentration or dissolution of the drug in presence of polymers. The four polymers namely Carbomer 934 (CP), Povidone K-30 (PVP), Poly Ethylene Glycol (PEG) and Hydroxy Propyl Methyl Cellulose (HPMC) were selected for the present study to observe their effect on the concentration of Pantoprazole (PP), which have shown promising results. The data obtained have shown that PVP and CP have exhibited excellent results wherein, in presence of PVP the dissolution of the drug has been consistently stable with time which indicated that in presence of PVP the dissolution of drug remains constant with time and hence remains un-dissolved as floating state for a long time indicating that for floating retention time PP increases in presence of PVP. The data obtained with CP have indicated that the concentration or dissolution of PP decreases in presence of CP, even more decreases in comparison to control which indicated that in presence of CP the floating retention time of PP increases with time and remains un-dissolved for long time, thus, CP and PVP have been the polymers showing excellent results for increasing the floating retention time of the drug. Other polymers namely HPMC and PEG however did not show considerable effects on the floating retention time of drug PP. The results have been presented in bar graphs (table 1 to 3) and line graphs (table 1 to 3), wherein, it has also been observed that increasing the quantity of polymers 1:1 (PP: polymer), 1:2 (PP: polymer) and 1:3 (PP: polymer) did not exhibit any considerable effect on floating retention time of PP which indicates that the effect of polymers on floating retention time of drug is independent of their concentration. The results obtained have also indicated that the bioavailability of the drug will be increased in stomach as there is a direct correlation between the floating retention time and bioavailability of the drug. Thus, the study has become encouraging as the aims and objectives of problem selected have been obtained promising.

Effect of polymer quantity on the Retention time of the drug

The studies have shown that the variable quantities of the polymer (40, 80 and 120 mg) with drug (40 mg) did not exhibit any considerable and significant effect on the Retention time of the drug (Line graphs- 4-7). However, it has been observed that polymer-3 (PVP: Povidone K-30) showed a high degree in decrease of retention time of the drug at 40 mg in comparison to 80 and 120 mg (Line graph- 5).

CONCLUSION

The present study of preparation of floating drug of pantoprazole with different polymers namely Carbomer 934 (CP), Povidone K-30 (PVP), Poly Ethylene Glycol (PEG) and Hydroxy Propyl Methyl Cellulose (HPMC) has revealed that the floating retention time of the drug has increased significantly in comparison to non-floating drug. It has been observed that out of four polymers only two polymers namely Carbomer 934 (CP), Povidone K-30 (PVP) have shown excellent increase in floating retention time of the drug. Moreover, Carbomer 934 (CP) has shown a greater increase of floating retention time. It has been established that if the floating retention time of any drug is increased, the bioavailability of the drug in the stomach will also increase. The present study is of immense importance in the sense that such floating drugs for the treatment and management of erosion and ulceration will be available in the stomach for long time. Thus, the present study will provide better formulations for the treatment of such stomach and gastric problems.

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